PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference QUETI-SYNR	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/FI2004/000560	International filing date *(day/month/year)* 23.09.2004	Priority date *(day/month/year)* 23.09.2003
International Patent Classification (IPC) or national classification and IPC C07D281/16, C07D295/18		
Applicant FERMION OY		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23.06.2005	09.08.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Härtinger, S Telephone No. +49 89 2399- 8289

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FI2004/000560

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-10 as originally filed

   Claims, Numbers

   1-10 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V:

1. The invention relates to a method for the preparation of the dibenzothiazepine compound (I) by ring formation of 2-piperazinoyl-anilino-sulfides of the general formula (II).

   The relevant prior art has been cited in the International search report.
   D1: US-A-3 539 573 (JEAN SCHMUTZ ET AL) 10 November 1970 (1970-11-10)
   D2: DATABASE BEILSTEIN CROSSFIRE BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT, MAIN, DE; Citation Number 5562436 1988, XP002316545
   D3: WARAWA E J ET AL: "Behavioral approach to nondyskinetic dopamine antagonists: Identification of Seroquel" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 44, 1 February 2001 (2001-02-01), pages 372-389, XP002213291 ISSN: 0022-2623
   D4: WO 02/083624 A (SCHERING CORPORATION; PHARMACOPEIA, INC) 24 October 2002 (2002-10-24)
   D5: WO 01/55125 A (EGIS GYOGYSZERGYAR RT; BOZSING, DANIEL; KOVANYINE LAX, GYOERGYI; SIMIG) 2 August 2001 (2001-08-02)

2. Process claims 1-4
   The patent D1 teaches how to obtain dibenzo[b,f]-1,4-thiazepine derivatives bearing a substituted piperazine ring at position 11. In column 6, a synthesis strategy is presented, which proceeds via the intramolecular condensation of amino substituted diphenyl-sulfide-acid amides (XIV), whereby POCl3 is suggested as a condensing agent. As an alternative, D1 also teaches the ring closure reaction of diphenyl-sulfide, wherein the amino group is further substituted by an piperazinoyl group (cf. formula XV). It is noted that this alternative has also be disclosed in D5(cf. claim 1). As hydroxyethoxyethyl substituted piperazine derivatives have not been used in cyclisation reactions, novelty is acknowledgeable over the cited prior art.

   However, the skilled person, who was looking for a novel route to the present compounds (I), would have considered the teaching of D1 as a convenient manner to achieve the dibenzothiazepine ring closure reaction. As the present compounds do

not bear substituents, which could interfere with the reactive groups involved in the process disclosed in D1 (and D3, D5), the skilled person would have expected that the analogous application to the present starting product (II) will likewise proceed in the desired manner. As D1 clearly sets out the scope of the reaction, wherein inter alia the piperazine moiety may be substituted with further hydroxyalkyl and alkoxyalkyl groups, and the further cited prior art confirms the general applicability, the application of the teaching of D1 to the present starting material is therefore an obvious choice, which does not involve an inventive step in the sense of Art. 33(3) PCT.

3. Intermediate according to claim 10
The present intermediate (III) relates to the hydroxy group protected precursors of the final product (I). Given the presently proposed reaction path, which embraces intermediates having functional groups with comparable reactivity (OH, NH2), the necessity to protect the terminal hydroxy group by suitable protecting groups is obvious to the skilled person in the art. The compounds used in reaction step h on page 378 of D3, demonstrate that the acyl group is a suitable protecting group employed in analogous dibenzothiazine intermediates with a further substituent at the said benzo part. Hence, the use of acyl protected precursors in the preparation of the final product (I) is not considered to have involved an inventive step in the sense of Art. 33(3) PCT.

4. Intermediates according to claims 5-9
The document D2 (see Reaction ID 3389000 of the cited Database record) teaches how to obtain the genus of the key-intermediate employed in the above discussed synthesis route of D1. In plain analogy to this prior art, which differs merely by the peripheral substituent to the piperazine ring, an ortho-iodobenzoyl-piperazine is coupled to aminothiophenol to give the said key-intermediate. In the light of the teaching of D1, the use of a starting material having the present formula IV is considered to be an obvious choice for the skilled person, who was putting into practice the teaching of D1. By consequence, the subject-matter of claim 5 does not appear to have met the requirements of Art. 33(3) PCT.

As to the subject-matter of claim 6 (unprotected OH) and claims 7-9 (protected OH),

the requirements of Art. 33(3) PCT have not been met for analogous reasons.